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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,462	05/01/2001	Jehad Charo	1430-264	7394

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EXAMINER	
KATCHEVES, KONSTANTINA T	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,462	CHARO ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 26* is/are allowed.

6)☒ Claim(s) *1-13 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending in the present application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 24 May 2004 has been entered.

Response to Arguments

Claims 1-9, 11-13 and 24 stand rejected under 35 U.S.C. 103(a) over Rhodes (US 5,508,310) in view of Hermann et al. (US 5,620,896) for the reasons of record and those set forth below.

Applicants' arguments filed 28 July 2004 and declaration filed 2 February 2002 have been fully considered but they are not persuasive.

Applicant maintains the position that "the different mechanisms and objectives of protein vaccines and DNA vaccines do not support the use of a Schiff base forming compound as an adjuvant for DNA vaccines based on its use as an adjuvant for protein vaccines." The examiner already rebutted this argument in the final rejection mailed 13 February 2004. T

As discussed previously, Applicants assert that there were good reasons to have believed that tucaresol would not work in the setting of a DNA vaccine, hence, there is no expectation of

success. Applicants state that the immune responses elicited by protein vaccine (both viral and non-viral micro-organisms) utilizes mechanism illustrated by either pathway A or B (attached figure), whereas immune responses elicited by DNA vaccine utilize a unique mechanism of antigen handling that involves neither A or B. Applicants regard the major difference between the two is that the wild type infection involves an array of danger signals and co-stimulatory signals initiated by pathogen associated molecular patterns during the uptake/entry phase to APC which is not presented in DNA vaccine. Applicants assert that adjuvants and tucaresol work on co-stimulatory mechanisms and do not affect the recognition of antigen by the T cell receptor or the signal it transduces. Applicants further assert that the co-stimulatory environment associated with DNA vaccination is absent or very weak compare to the one associate with conventional protein vaccine, hence tucaresol is only effective in pathway A and B, but not in DNA vaccine. Applicants also indicate the surprising feature of the invention is the demonstration of a TH2 response instead of TH1 response as reported earlier. Applicants reiterate their comments that known immuno-potentiating agents have been tried with DNA vaccination with limited success, whereas conventional adjuvants such as alum are not effective with DNA vaccination. Applicants further argue that Herrman et al. do not disclose particular adjuvants which might expect to work in DNA vaccination. Applicants ask the Examiner to provide evidence for the statement that "signal 1 is considered the same for natural infection, conventional vaccines and DNA vaccines," and "protein antigens can be secreted by transfected cells and then taken up by antigen presenting cells." Therefore, Applicants conclude that the combination of Rhode and Herrman references do not suggest a reasonable expectation of success to use tucaresol as adjuvant in DNA vaccination.

Applicants' argument has been fully considered but deemed not persuasive. The Examiner acknowledges that not every known immuno-potentiating agents that functions in protein vaccination would be effective in DNA vaccination, however, there is sufficient teaching to support that there is a reasonable expectation of success that tucaresol would potentiate immune response with DNA vaccination. As discussed previously, Rhodes et al. teach that the mechanism by which the Schiff base-forming compounds (including tucaresol) influence immune responses is by reacting with amino groups on the surface of lymphocytes and antigen presenting cells, thereby provide co-stimulation to T-cells, amplifying the co-stimulation provided by physiological Schiff base-formation between ligands on the surface of cells (see col.16, lines 49-56). In addition, reference 10 cited by Applicants (Rhodes et al 1995) teaches that convergence of Schiff base signaling with TCR signaling has been identified at the level of tyrosyl phosphorylation of the MAP-kinase ERK2 (see page 73, bottom of 1st col. through top of 2nd col). Therefore, tucaresol provide immuno-potentiating response by direct engaging T cells and providing signals that converges with signal 1 result from TCR-antigen ligation. This signal 1 is considered same for natural infection, conventional vaccines and DNA vaccines (see Figure D, legend). This statement is in the legend of Figure D provided by Applicants.

Applicants assert that Figure C represents the delivery of antigen as DNA that differs from pathway A and B in which the antigen is taken up either by viral receptor or endocytosis. However, protein antigen encoded by DNA can also be secreted from the cell (the claims have no limitation on what cell type the DNA is introduced) and subsequently taken up by antigen presenting cells, and produce a MHC class II response which resembles the pathway illustrated in Figure B. The level of skill in the relevant art is high. Producing nucleic acid sequence

encoding an antigen with a secretory signal is routinely done. Therefore, by forming Schiff base directly with CD4+ T cell, thus amplifying co-stimulatory effects provided by physiological Schiff base formation between ligands on the surface of the cells, there is reasonable expectation that tucaresol would enhance immune response elicited by the antigen.

The Examiner acknowledges that Applicants have demonstrated that co-administration of tucaresol and DNA encoding HSP-65 elicits TH2 mediated antibody response in addition to previously reported TH1 response. However, this finding is not a limitation in the presently claimed invention.

It would have been obvious to use Schiff base forming compound such as tucaresol to enhance immune response to DNA vaccination because of the combination teaching of Rhodes et al and Herrman et al. as discussed in the two previous office action. Rhodes et al. has demonstrated that tucaresol increased T-lymphocyte priming to antigen and increased antibody production (see Figure 1-7). Rhodes et al. teach that these compounds can be used as a vaccine adjuvant (see col. 9, lines 38-40). This notion is also reiterated in reference 10 cited by Applicants (Rhodes 1995, page 73, top left). Therefore, Applicants does not provide sufficient evidence that tucaresol would not function as a vaccine adjuvant in the setting of DNA vaccination. Rather, Applicants assert that co-stimulatory environment is absent or weak in the case of DNA vaccine. This should provide additional motivation for one of ordinary skill of art to use Schiff base forming compound to potentiate immune response because this class of compound specifically enhance co-stimulatory effect. As such, the claimed invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Regarding the declaration of Dr. Rhodes, the declaration primarily avers the opinion that the mechanisms of DNA and peptides differ such that the invention would not have been obvious to one of skill in the art. This position is rebutted in detailed above. Additionally, the declaration states that there was an opinion that held by those in the art adjuvants used in protein vaccines would differ than those used in DNA vaccines. These opinions by Dr. Rhodes does not overcome the *prima facie* case of obviousness set forth in the non-final rejection of 16 July 2002 and 11 March 2003. Applicant should note that the scope of the claims does not exclude a peptide within the vaccine formulation such that one of skill in the art would consider adjuvants that have been used in the art with peptide vaccines. Also, the declaration is an opinion declaration and does not show data regarding any unexpected results.

The opinion of Dr. Rhodes indicates that since absolute success was not possible based on the art cited by the examiner such that the invention could not have been obvious to one of ordinary skill in the art at the time the invention was made. In particular, Dr. Rhodes states that: "that adjuvants were likely to be needed for DNA vaccination and there was an expectation that. Because of the fundamental differences between DNA vaccination and other forms of vaccination (e.g., using protein vaccines), adjuvants that worked for conventional protein vaccines would be unlikely to work for DNA vaccines (ref. 8 of Appendix 1)." Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co* ., 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v.*

American Hoist & Derrick Co ., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); *In re Papesch* , 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi* , 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton* , 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). Therefore, for the reasons discussed in detail above and the non-final rejections of 16 July 2002 and 11 March 2003 the information in the Rhodes reference when combined with the Hermann et al. reference provided such a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER